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10/729,387	12/08/2003	Francis J. Giles	PHARMA-139	8138

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EXAMINER	
DELACROIX MUIRHEI, CYBILLE	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,387	GILES ET AL.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 08 December 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Claims 1-25 are presented for prosecution on the merits.

Information Disclosure Statement(s)

Applicant's information disclosure statements received Oct. 27, 2004 and June 21, 2004 have been considered. Please refer to Applicant's copies of the 1449s submitted herewith.

Claim Objection(s)

1. Claims 1, 14, 15, 17-23, 24 are objected to because of the following informalities: In claims 1, 14, 15, 24, the phrase "selected from the group comprising" is improper Markush terminology. The phrase should read –selected from the group consisting of--. Please see MPEP 2173.05(h). Also in claim 14, line 12, after "inhibitor", the term "and" should be deleted and replaced with –wherein--. Appropriate correction is required.

Claims 17-23 are presented in an awkward manner. For example, claims 17-18 may be rewritten to read –The method of claim 15, wherein the leukemia is acute myelogenous leukemia or chronic myelogenous leukemia.—

Claims 19-23 may be rewritten to read (claim 20) –The method according to claim 15, wherein the patient has refractory/relapsed leukemia and has been previously treated with imatinib mesylate (STI-571).-- Please refer to the claims USPN '6,645,972 for guidance.

Claim Rejection(s)—35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of leukemia, does not reasonably provide enablement for treatment of all types and forms of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The claims are drawn to a method for treating a patient having cancer, other than leukemia, which comprises administering an effective amount of a compound of Formula (I) and a Bcr-Abl tyrosine kinase inhibitor along with an additional chemotherapeutic agent to the patient.

(2) The state of the prior art

With respect to cancer, this a broad term which encompasses numerous forms of

neoplastic diseases, each involving different types of tissues and organs and also includes blood borne diseases. As recognized in the art, many different anti-neoplastic drugs are used to treat a variety of cancers, but there is no one drug or one drug combination, which is capable of treating all cancers in general. Please see pages 1226-1229 of Goodman & Gilman's.

Additionally, the prior art recognizes the use of imatinib (GLEEVEC) for the treatment of leukemias as well as some other tumors such as ovarian, prostate, breast lung cancer and gliomas (WO 99/03854, page 17). Chu et al., recognizes inhibitory activity of troxatyl against cancers such as lung, ovarian, renal, prostate, breast, colon, leukemia, melanoma and CNS cancer. Please see col. 14, Table 2.

(3) The relative skill of those in the art

The relative skill of those in the art is high. However, given the state of the art as set forth above, the artisan is currently unaware of any one particular anticancer agent or combination of agents that is effective against all cancer cell types.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical and cancer art is high. Additionally, the lack of significant guidance from the present specification or prior art with regard to the actual treatment of all cancer cell types in a mammal, including a human, with the claimed compounds as the active ingredient makes practicing the claimed method unpredictable.

(5) The breadth of the claims

The complex nature of the subject matter to which the present claim is directed is exacerbated by the breadth of the claim. The claim is broad and encompasses treatment of a vast number of possible cancer types including solid tumors as well as blood borne tumors.

(6) The amount of direction or guidance presented

Applicant's specification appears to only be enabled for the treatment of leukemia. It does not enable one of ordinary skill in the art to use the claimed invention in the treatment of the numerous neoplastic diseases covered by the term "cancer." Applicant's specification does not set forth a representative number of examples of cancers, which would be treated by the claimed compound.

(7) The presence or absence of working examples

The working examples in the specification involve only the use chronic myelogenous leukemia cell lines as well as in vivo examples using mice implanted with the leukemia cell lines. Please pages 23-27.

(8) The quantity of experimentation necessary

Since (1) the prior art recognizes that no one compound or combination of compounds is capable of treating the vast number of possible cancerous diseases encompassed by the term "cancer"; (2) the prior art recognizes activity of the claimed compounds against a limited number of cancer types; (3) the specification shows anti-tumor activity only against leukemia cell lines and (4) since the claims are very broad and include treatment of any type of cancer ranging from solid cancers to blood-borne cancers, one of ordinary skill in the art would be burdened with undue experimentation

to determine which cancers would be treated by administration of the claimed compounds.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 16 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 recites the limitation "the ratio" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 23 recites the limitation "said combination" in line 7. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejection(s)—35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 1-5, 7, 11, 14-15, 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Nada et al.

Nada et al. disclose a synergistic pharmaceutical combination comprising Troxatyl and STI-571. Nada et al. teach that the combination demonstrated synergistic activity against CML cell lines.

Nada et al. additionally disclose a method of treating mice having CML by administering to the mice a combination of Troxatyl and STI-571. The combination suggested synergistic activity. Please refer to the abstract.

Claim Rejection(s)—35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jolivet et al., 6,645,972.

Jolivet et al. disclose a method of treating a patient suffering from leukemia and who has been previously treated with a Bcr-Abl tyrosine kinase inhibitor such as STI-571, wherein the method comprises administering to the patient an effective amount of a pharmaceutical composition containing at least one compound of Formula (I) (preferably (β-L OddC) or (5-Fddc)). In another embodiment the method provides for treatment of a patient with leukemia that has become resistant to the Bcr-Abl tyrosine kinase inhibitor (STI-571), wherein the method comprises administering to the patient an effective amount of a composition containing at least one compound of Formula (I). The compounds of Formula (I) are in the form of the (-) enantiomer at least 97% free of the corresponding (+)enantiomer. Furthermore, the ratio of (β-L OddC) or (5-Fddc) to STI-571 is 1:250 to 250:1, 1:50 to 50:1, preferably 1:20 to 20:1. Other types of leukemia that may be treated are acute myelogenous leukemia, chronic myelogenous leukemia (in blastic phase) or multidrug resistant leukemia. Finally, the pharmaceutical formulations containing suitable excipients along with the compounds of Formula (I) are also taught. Please see col. 4-col. 9.

Jolivet et al. do not specifically disclose administering at least one compound of Formula (I) in combination with a Bcr-Abl tyrosine kinase inhibitor such as STI-571. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the method and composition to include such a combination because Jolivet et al. teach that STI-571 demonstrates significant activity

against leukemia, especially chronic myelogenous leukemia, and one of ordinary skill in the art would reasonably expect the combination of the two anti-leukemic compounds to treat the patients suffering from leukemia. Furthermore, such a modification would have been motivated by the reasonable expectation that the combination would act together to treat the cancer or that should resistance to STI-571 develop the compounds of Formula (I) would be active against the leukemia thereby treating the patient.

6. Claims 1-23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gourdeau et al., WO 00/57861 in view of FDA article.

Gourdeau et al. disclose a method of treating leukemia (AML, CML, etc.) as well as all subtypes of leukemia in a patient in need thereof by administering to the patient an effective amount of a compound represented by Formula (I), more specifically, the compound (β-L-oddC), i.e. troxacitabine, or (5-FddC) or a salt thereof. The compounds of Formula (I) are administered (intravenously) to the patient by continuous infusion at a dosage of 0.01 to about 5.0 mg/kg/hour. Gourdeau et al. also teach administering the compounds of Formula (I) wherein the compounds are at least 97% free of the corresponding (+) enantiomer. The method also involves administering a pharmaceutical composition containing a compound of Formula (I) together with at least one pharmaceutically acceptable carrier or excipient. Please see pages 4-7, page 9, page 11 ; pages 15-17.

Gourdeau et al. do not disclose a method of treating leukemia by administering a pharmaceutical composition containing a combination of a compound of Formula (I) and a Bcr-Abl tyrosine kinase inhibitor such as STI-571. However, the Examiner refers to the

FDA article, which disclose that STI-571 has been approved for treatment of leukemia (CML). Please see the article.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method and composition of Gourdeau et al. to combine the compounds of Formula (I) with STI-571 for the treatment of leukemia because one of ordinary skill in the art would reasonably expect at least an additive effect of the two anti-leukemic compounds to effectively treat patients suffering from leukemia. Furthermore, concerning treatment of STI-571 resistant leukemia, such a modification would have been motivated by the reasonable expectation that should resistance to STI-571 develop the compounds of Formula (I) would continue to be active against the leukemia thereby treating the patient.

Concerning the claimed ratios of the compound of Formula (I) and STI-571, since efficacy of the compounds depends on the dosage or concentration administered, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the method and composition of the prior art such that the compounds are present in a ratio or amount effective to treat the leukemia.

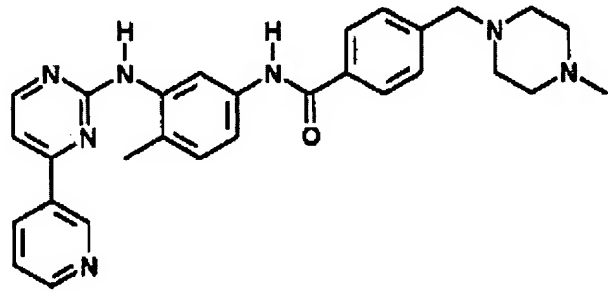
7. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chu et al., 5,817,667 in view of Zimmerman et al., WO 99/03854

Chu et al. teach a method of treating cancers such as a pancreatic cancer, leukemia, prostate cancer breast cancer, ovarian cancer etc., the method comprising administering (intravenously) an effective amount of (-)-OddC, i.e. troxacitabine, or a salt thereof to a patient in need thereof. Chu et al. additionally disclose that (-)-OddC

can also be administered in combination with other known anticancer agents. Please see col. 3, lines 10-52; col. 10, lines 54-61.

Chu et al. do not disclose administering troxacitabine and the additional anti-cancer agent in combination with a Bcr-Abl tyrosine kinase inhibitor. Yet, the Examiner refers to Zimmerman et al., which disclose a method of treating tumor diseases such as gliomas, sarcomas, prostate tumors, colon tumors, breast tumors and tumors of the ovary by administering to a patient in need thereof an effective amount of a compound of Formula (I)

1. A form of the methanesulfonic acid addition salt of a compound of formula I,



(I)

comprising crystals of the β-modification.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the method of Chu et al. by additionally administering the compound of Formula (I) as disclosed by Zimmerman because one of ordinary skill in the art would reasonably expect the combined action of the anti-tumor compounds to be effective in treating the cancerous tumors in the patient.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 15-23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,645,972. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and the claims of USPN '972 claim methods of treating leukemia in a patient by administering an effective amount of the compound of Formula (I) and a Bcr-Abl tyrosine kinase inhibitor.

The claims of the instant application differ from the claims of USPN '972 in that USPN '972 claim a method of treating leukemia by administering the compound of Formula (I) to a patient who has previously been treated with STI-571 (claim 1) or administering the compound of Formula (I) to a patient who has been previously treated with STI-571 and has become resistant to STI-571 (claim 2).

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the claimed methods to administer a combination of the compound of Formula (I) and the Bcr-Abl tyrosine kinase inhibitor (STI-571)

because one of ordinary skill in the art would reasonably expect the combination of the two anti-leukemic compounds to treat the patients suffering from leukemia. Furthermore, such a modification would have been motivated by the reasonable expectation that the combination would act together to treat the cancer or that should resistance to STI-571 develop the compounds of Formula (I) would be active against the leukemia thereby treating the patient.

Conclusion

Claims 1-25 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Cybille Delacroix-Muirheid** whose telephone number is **571-272-0572**. The examiner can normally be reached on Mon-Thurs. from 8:30 to 6:00 as well as every other Friday from 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Christopher Low**, can be reached on **571-272-0951**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM
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